Acid-Catalysed Reactions

The present invention relates to acid-catalysed reactions for producing alkenes, ethers, acetals or ketals. Specifically the present invention relates to reactions for the formation of alkenes, ethers (including cyclic ethers), acetals and ketals in the presence of heterogeneous acid catalysts under near-critical or supercritical conditions.

In particular, the present invention seeks to provide improved acid-catalysed reactions of alcohols (whether aliphatic, aromatic or heterocyclic) to produce ethers, alkenes, acetals or ketals as required.

The use of acid catalysis in industry is widespread and of importance.

We have shown that reactions of industrial importance such as ether, acetal, ketal and alkene formation can be carried out under supercritical or near critical conditions of temperature and pressure using a heterogeneous acid catalyst with significant advantages. Their use in supercritical fluids has not previously been described.

Using supercritical fluids as a solvent eliminates the need for conventional organic solvents and hence gives environmental benefits. However, a more important consequence is that the reactions can be modified by using supercritical fluids to give surprisingly high yields and/or selectivities.

We have also found that certain products which are not easily accessible by conventional routes can be obtained more easily using the process of the present invention. Thus, whilst rearrangements may occur in conventional reactions we have found that certain reactions can be carried out under the conditions of

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the present invention without any significant
rearrangement occurring. For example, ether formation
in supercritical fluids under the conditions of the
present invention can give rise to enhanced yields of
n-alkyl ethers rather than the branched products which
are obtained in conventional procedures.

Ethers

Conventionally, the formation of ethers can be
carried out via a wide number of classical routes .e.g.
Williamson Synthesis, dehydration of alcohols,
alkylation of alcohols with inorganic esters, and
alkylation with diazo compounds.

In the Williamson synthesis an alkyl halide is
reacted with an alkoxide or aryloxide. This reaction
therefore involves preforming the alkoxide from an
alcohol by reaction with a strong base and subsequent
reaction with an alkyl halide. This results in the
generation of an equimolar amount of a halide salt
which then must be disposed of. There are also the
hazards associated with the handling of the alkyl
halide in the case of volatile and/or toxic halides
such as methyl iodide which is both a known carcinogen
and very volatile.

In the case of reactions of alcohols with
inorganic esters (e.g. the reaction of an alcohol with
dimethyl sulfate), the inorganic esters are usually
highly toxic. Again the alcohol has to be converted to
the alkoxide using a strong base prior to the reaction.
A further problem is the disposal of the aqueous
effluent which can contain large amounts of inorganic
salts.

The reaction of diazo compounds with alcohols is a
cleaner reaction but suffers from the dangers

associated with the thermal decomposition of diazo
compounds. Also, diazo compounds are expensive and so
it is not practicable to carry out this reaction on an
industrial scale except for very high value products.

One of the most cost-effective and atom-efficient
processes for producing ethers is the dehydration of
alcohols using an acid catalyst. This reaction is
usually carried out in the liquid phase but suffers the
drawback that, in the reaction of n-alcohols, the
alcohol can rearrange from the primary to secondary and
then to the tertiary carbocation, thereby giving a
mixture of products. A further problem is that the use
of homogeneous catalysts such as sulphuric acid require
a separation or neutralisation step at the end of the
process. The use of homogeneous catalysts means that
these processes are usually carried out in batch or
semi-batch reactors. The use of batch systems also
gives increased down time for charging and discharging.
There is also the disadvantage that the product will be
a mixture of thermodynamic and kinetic products due to
relatively long residence times in the reactor.
Distillation or some other physical means of separation
is therefore usually required to separate the products.

A number of other reactions are also carried out
to form ethers, usually on a smaller scale, such as the
reaction of a Grignard reagent with an acetal or
cyclisation of alcohols with lead, silver or mercury
salts all of which suffer from high cost and problems
of waste disposal.

Acetals and Ketals

The most widely used method of formation of
acetals and ketals is the reaction of alcohols with
aldehydes or ketones under acidic conditions which

involves the removal of water. These reactions are
usually carried out in an excess of the alcohol or in
an inert solvent. The conventional process therefore
presents the problem of removing excess reagent and the
catalyst must also be separated from the mixture if a
homogenous catalyst is used.

Alkenes
    The industrial preparation of alkenes is normally
carried out by dehydrogenation over noble metal
catalysts or cracking reactions or dehydration
reactions using inorganic acids. Such reactions
present the problems of removal of catalyst, reaction
solvent and distillation to purify products.

    We have found that the use of supercritical fluids
for the replacement of conventional solvents not only
has significant environmental benefits but also leads
to cleaner, higher yielding reactions.
    Although the mechanism of the reactions is not
fully understood it is believed that mass transport
effects play a role in the observed improvements in
yield and/or product selectivity. Surprisingly, the
use of a heterogeneous catalyst in place of a
homogeneous catalyst under near-critical or
supercritical reaction conditions does not render the
reaction ineffective. Instead we have found that the
reactions benefit from improved yields and/or
selectivity in product formation. This is so despite
the expectation that the relatively severe conditions
at or near the supercritical point of the reaction
medium may give rise to a mixture of products because
the reactants have sufficient energy to react via
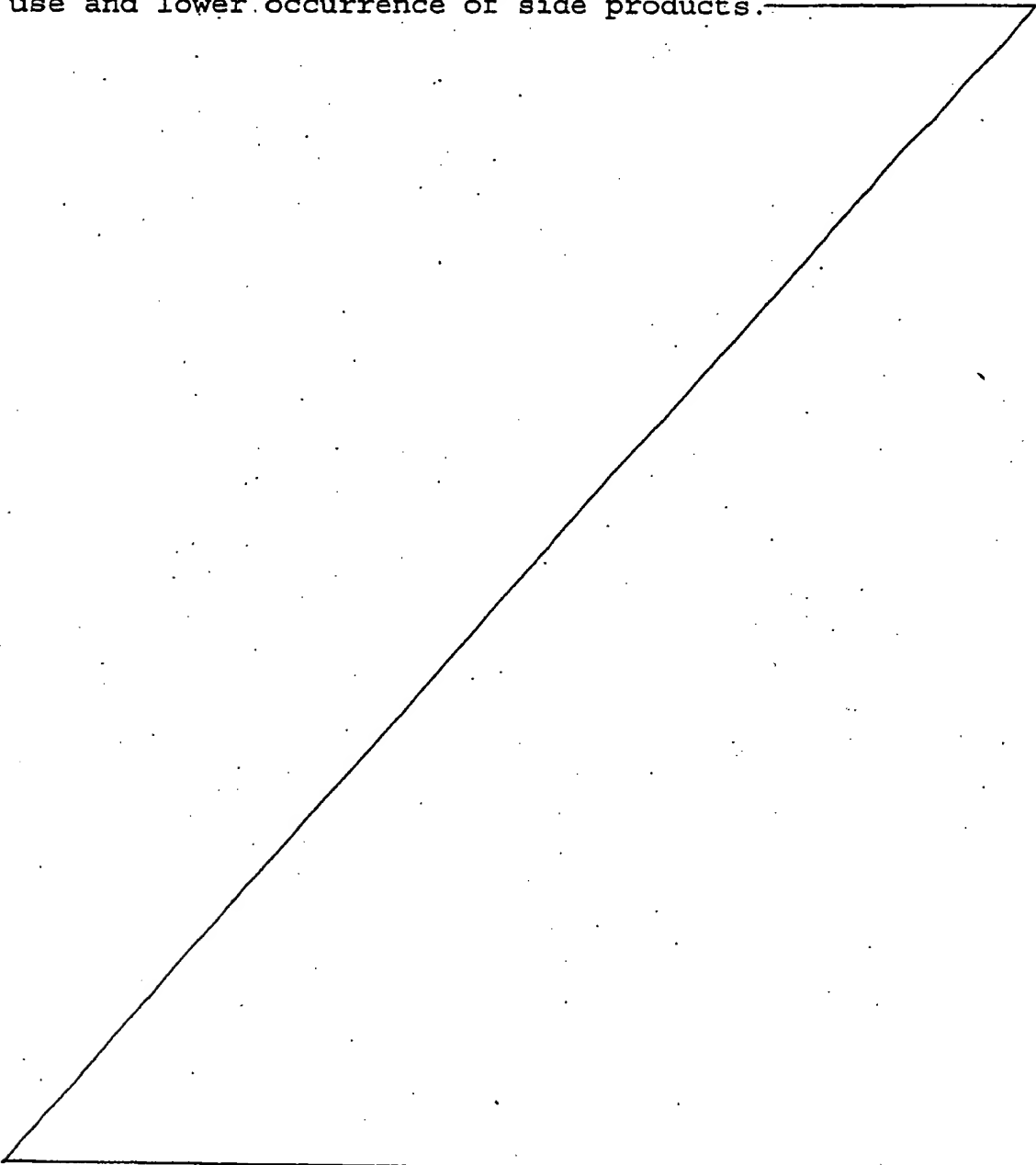several different pathways.

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One consequence of using the heterogeneous catalyst is that there is no need for complicated separation procedures to liberate the product from the reaction mixture and catalyst. This represents quite a benefit in terms of both the time savings and cost savings of the present invention.

We have thus found that it is possible by using a combination of supercritical fluids and a heterogeneous catalyst (e.g. the Deloxan ASP catalyst from Degussa or Acidic Amberlyst resin from Rohm and Haas) in a continuous flow reactor to carry out a number of reactions rapidly and cleanly. These reactions can often be performed in high yield and take place under near-critical or supercritical conditions.

According to the present invention, there is provided A process in which a hydroxyl-substituted organic compound selected from the formulae R_1CH_2OH, R^1R^2CHOH and $R^1R^2R^3COH$ is exposed, optionally in the presence of one or more further organic compounds selected from second hydroxyl-substituted organic compounds of the formulae R^4CH_2OH, R^5R^6CHOH, and $R^7R^8R^9COH$ and carbonyl compounds of the formula $R^{10}R^{11}CO$, to a heterogeneous catalyst which is able to provide a source of acid in a continuous flow reactor under supercritical conditions or at near-critical conditions for the fluid that is acting as solvent, with the result that an ether is formed from two hydroxyl-substituted organic compound molecules in a dehydration reaction, an acetal or ketal is formed by reaction between a hydroxyl-substituted organic compound molecule and a molecule of a said carbonyl compound and an alkene product is produced by dehydration of a single hydroxyl-substituted organic compound molecule, wherein the conditions of temperature, pressure, and flow rate are controlled according to the product to be obtained, and wherein each of R^1 to R^{11} is independently

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selected from: hydrogen or hydroxyl; an optionally
substituted alkyl, alkenyl, alkynyl, aralkyl,
cycloalkyl, cycloalkenyl, or aryl; or a heterocyclic
group.

5   Aliphatic and aromatic alcohols are preferred
because they give cleaner reactions, with aliphatic
alcohols being most preferred on the grounds of ease of
use and lower occurrence of side products.

It is preferred that each of R^1 to R^{11} when present is an alkyl group which may be optionally substituted. Since the process of the present invention is applicable to diols, triols and higher alcohols as well as alcohols, it is particularly preferred that the optional substituent, when present, on one of the groups R^1 to R^{11} is hydroxyl. It is also preferable, in order to avoid the risk of unwanted side products, that the total number of alcohol groups within the organic compound does not exceed three.

When any of the R^1 to R^{11} groups are optionally substituted, the substituent groups which are optionally present may be any conventional substituent provided that any such substituent is not incompatible with alcohol functionality or with the reaction conditions.

Generally, when any of the R^1 to R^{11} groups represents an optionally substituted alkyl group each group may independently be linear or branched and suitably contain 1 to 10, preferably 1 to 6 carbon atoms in the carbon chain, not including any optional substituent which may be present.

In relation to alkyl groups, specific examples of such optional substituents include halogen atoms and nitro, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl (especially CF_3), C_{1-4} alkoxy, C_{1-4} haloalkoxy and (C_{1-4} alkoxy) carbonyl groups. Of these, hydroxyl and C_{1-4} haloalkyl are preferred. It is preferred, however, that when any of groups R^1 to R^{11} is alkyl that the alkyl moiety is unsubstituted.

In relation to a phenyl moiety, optional substituents include halogen atoms, and nitro, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl (especially CF_3) and C_{1-4} alkoxy groups.

In general, 1 to 3 optional substituents may suitably be employed. Halogen atoms when present are preferably fluorine.

Where the starting materials for the reaction may exist in isomeric form the reaction of the present invention is applicable to all such optical or geometric isomers.

Suitable catalysts include Deloxan acid catalysts (Ex. Degussa-Hüls AG), zeolites, metal oxides, molecular sieves, clays, sulfonic acid derivatives, or other equivalent heterogeneous sources of a Brønsted acid (e.g. Amberlyst resin). The catalyst is ideally supported on an inert carrier. Preferably the catalyst contains sulfonic acid groups, and more preferably the catalyst is a Deloxan catalyst or an equivalent thereof.

The reactions of the present invention are preferably carried out in a single homogeneous phase. However, in reactions where water is generated this may separate out as a separate phase. This separation can be helpful to the reaction. Preferably, the reactions are performed in the supercritical phase.

In the context of the present invention, the lower limit suitable for supporting the reaction is a condition of temperature and pressure below or near to (perhaps at) the critical point of the solvent. When a fluid reaches its critical point its density is substantially decreased relative to its density at its boiling point at normal pressure. Small changes in pressure or temperature near the critical point cause additional changes in density. The process of the present invention will operate in the fluid at temperatures and pressures below the critical point but at which the density is sufficient to ensure solvation

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of reagents.

The upper limit of temperature and pressure is governed only by limitations of the apparatus.

In practice, the choice of the near critical or supercritical fluid will depend upon the solubility of the organic compound in the fluid since a function of the supercritical or near-critical fluid is to act as a solvent for the reagents. In some cases, however, it may be particularly convenient for the near-critical or supercritical medium to be simply the alcohol itself (and the other optional reactants when present). However, the use of a separate near-critical or supercritical fluid is generally preferred.

Particularly favoured media include carbon dioxide, alkanes such as ethane, propane and butane, alkenes, and saturated halocarbons such as hydroflorocarbons and trichlorofluoromethane.

The near-critical or supercritical reaction medium when present, may be a mixture of two or more fluids having critical points which do not require commercially unacceptable conditions of temperature and pressure in order to achieve the necessary conditions for reaction according to the present invention. For example, a mixture of carbon dioxide with an alkane such as propane may be employed close to or above the theoretical critical point of the mixture.

The alcohol starting material, if not a free-flowing liquid in its normal state may be dissolved in a solvent for the purpose of introducing the alcohol into the reactor. This solvent may be present in addition to or in place of the solvent which is to be the supercritical or near-critical reaction medium. Alternatively as stated above, the alcohol itself, and any further optional components of the reaction

mixture, may be the near-critical or supercritical
reaction medium.

Product formation may be monitored *in-situ* by
means of IR spectroscopy using a suitably positioned IR
cell, or by gas or liquid chromatography performed on
samples drawn from the reactor periodically.

We are thus able to form ethers from primary and
secondary alcohols with high conversion and good
selectivity for *n*, or branched, products. Surprisingly
n,n ethers can be formed by dehydration of *n*-alcohols
with little or no rearrangement. In the case of
phenolic compounds it is possible by altering the
reaction conditions to favour ether formation over
Friedel-Crafts alkylation and vice-versa.

We have also demonstrated that it is possible to
form acetals and ketals under similar supercritical or
near-critical conditions as those employed for ether
formation. In the case of branched alcohols, it is
also possible to select conditions in which the
corresponding alkene is obtained in high yield in
preference to the ether product.

There is also little requirement for excess
alcohols to be used in the process of the present
invention because of the excellent conversion rates;
this simplifies purification of the products.

The reactions are performed using a continuous
flow reactor (preferably tubular reactor). It is
therefore possible to control the residence time, and
also the other reaction parameters independently. This
allows greater control of the reaction resulting in
more efficient and also more selective reactions than
can be achieved in the conventional processes.

The present invention will now be described by way

of example only with reference to Figure 1. Figure 1
is a schematic diagram of a continuous flow reactor
according to the present invention.

The substrate 1, which is dissolved in an
appropriate inert solvent (for example an alkane such
as hexane) if it is not a free-flowing liquid or if it
is a solid, is pumped into mixer 2 which is a mixing
vessel. The mixer 2 may include a stirrer (not shown).
However, mixing of substrate 1 and fluid 3 may equally
be effected without the use of stirrer. The substrate
1 is mixed with fluid 3 which is delivered from a
reservoir via a pump to mixer 2. Where required, an
additional reagent can be added via the same or another
pump to mixer 2 with the ratio of the reagents being
independently varied as required.

The temperature and the pressure in the mixer is
adjusted to a temperature and pressure close to or
above the critical point of the fluid 3 as required.

Heating means are provided in the mixer for this
purpose. The mixture is then passed into reactor 5
which contains a heterogeneous catalyst (not shown)
fixed on a suitable support. A means of controlling
the pressure in the reactor is also included. The
catalyst provides a source of Brønsted acid to the
reaction mixture as the pressurised mixture passes over
the catalyst.

After an appropriate mean residence time in
reactor 5, the fluid 3, which now contains the product,
is passed into pressure reduction unit 6. The products
7 are removed via a take-off tap after passing through
pressure reduction unit 6. The flow rate of reactants
through reactor 5 is controlled by a valve (not
shown) in pressure reducer 6. Fluid 3 is vented
through a relief pipe 8 for subsequent recycling or

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disposal.

The parameters of a typical reaction might involve a system pressure of 40-300 bar (this will of course depend on the reaction medium) and the flow rate of the reagents is typically in the range of 0.5 to 20.0 ml/min. The reactor temperature is usually in the range of 30-350°C (again this will depend on the reaction medium) and the flow rate of supercritical or near critical fluid is usually in the range of 0.65 to 1.65 l/min of gaseous flow at atmospheric pressure-for a 10ml reactor.

The present invention will now be illustrated by the following examples in which the temperature is the catalyst bed temperature and the solvent flow is given as gaseous flow at atmosphere pressure.

Example 1

iso-Ether Formation

Isopropyl alcohol was exposed to a Deloxan ASP 1/7 acid catalyst (available from Degussa-Hüls AG) under the conditions given below in a continuous flow reactor. The volume of the reactor was 10 ml and the flow rate of the solvent was 0.65 L/min.
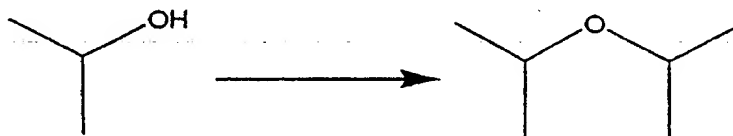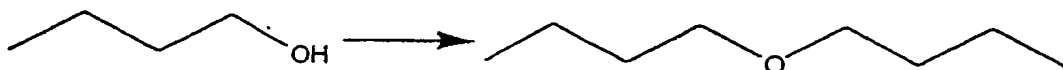

Temp (°C)	Pressure (Bar)	Substrate Flow Rate (ml/min)	Solvent	Yield (%)
200	200	0.5	CO_2	29

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Example 2

n-Ether Formation

n-Butanol was exposed to an Amberlyst 15 acid catalyst under the conditions given below in a continuous flow reactor. The volume of the reactor was 20 ml and the flow rate of the solvent was 0.65 L/min.
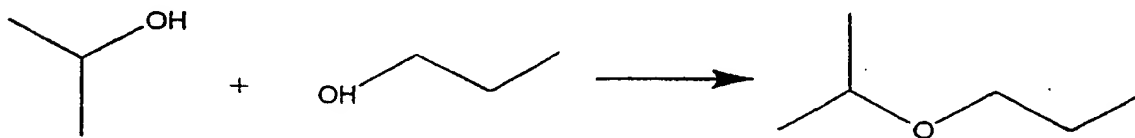

Temp (°C)	Pressure (Bar)	Substrate Flow Rate (ml/min)	Solvent	Yield (%)
200°C	200	0.5	CO_2	60

Example 3

Mixed Ether Formation

Isopropanol and n-propanol in the ratio of 1.2 parts isopropanol to 1.0 parts n-propanol were exposed to a Deloxan ASP 1/7 acid catalyst (Degussa-Hüls AG) under the conditions given below in a continuous flow reactor. The reactor volume was 20 ml and the flow rate of the solvent was 0.65 L/min.
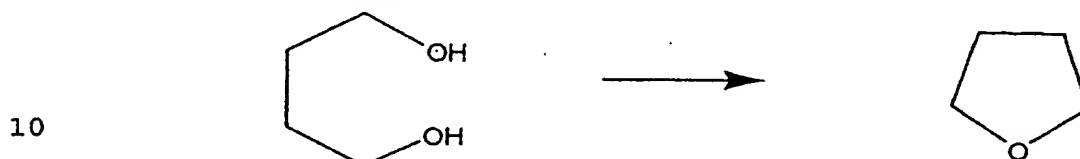

Temp (°C)	Pressure (Bar)	Substrate Flow Rate (ml/min)	Solvent	Yield (%)
150	200	0.5	CO_2	41

Example 4

Cyclic Ether

1,4-butanediol was exposed to a Deloxan ASP 1/7 acid catalyst (available from Degussa- Hüls AG) under the conditions given below in a continuous flow reactor. The reactor volume was 10ml and the solvent flow rate was 0.65 L/min.
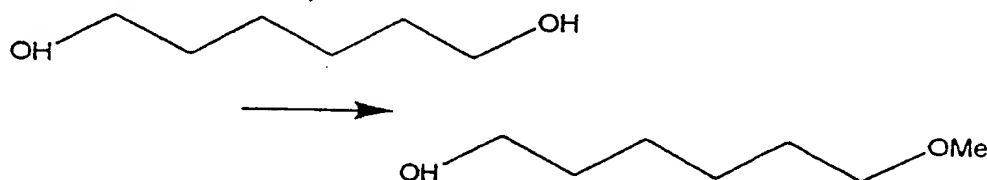

Temp(°C)	Pressure (atm)	Substrate Flow Rate(ml/min)	Solvent	Yield (%)
200	200	0.5	CO_2	100
150	100	0.5	CO^2	100
125	100	0.5	CO_2	87
200	100	2.0	CO_2	93

Example 5

Mono-Etherification of Diols

1,6-Hexanediol and methanol in the ratio of 1.0 part 1,6 hexanediol to 1.1 part methanol were exposed to a Deloxan ASP 1/7 acid catalyst (Degussa-Hüls AG) under the conditions given below in a continuous flow reactor. The reactor volume was 10 ml and the flow rate of the solvent was 0.65 L/min.

Temp(°C)	Pressure (atm)	Substrate Flow Rate(ml/min)	Solvent	Yield (%)	Di-ether (%)
100	200	0.5	CO_2	32	13
200	200	0.5	CO_2	65	6

Example 6

Acetal Formation

1,2-Ethanediol and benzaldehyde in the ratio of 2.0
parts benzaldehyde to 1.0 part 1,2-ethanediol were
exposed to a Deloxan ASP 1/7 acid catalyst (Degussa-Hüls AG)
under the conditions given below in a continuous flow
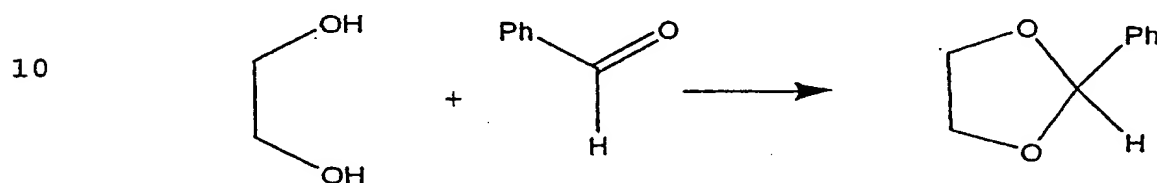reactor.   The reactor volume was 10 ml and the flow
rate of solvent was 0.65 L/min.

Temp (°C)	Pressure (atm)	Substrate Flow Rate (ml/min)	Solvent	Yield (%)
100	200	0.5	CO_2	89
200	200	0.5	CO_2	80

Example 7

Ketal Formation

1,2-Ethanediol and acetone in the ratio of 2.0 parts
acetone to 1.0 part 1,2 ethanediol were exposed to a
Deloxan c ASP 1/7 acid catalyst (Degussa-Hüls AG) under the
conditions given below in a continuous flow reactor.
The reactor volume was 10 ml and the flow rate of
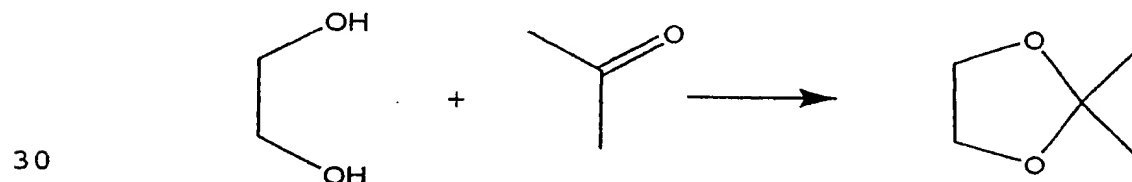solvent was 0.65 L/min.

Temp (°C)	Pressure (atm)	Substrate Flow Rate (ml/min)	Solvent	Yield (%)
150	200	0.5	CO_2	61

Example 8

Alkene Formation

2-Pentanol was exposed to a Deloxan ASP 1/7 catalyst (Degussa-Hüls AG) under the conditions given below in a continuous flow reactor. The reactor volume was 10ml and the flow rate of solvent was 0.65 L/min.

Temp (°C)	Pressure (atm)	Substrate Flow Rate (ml/min)	Solvent	Pentene (%)
200	200	0.5	CO_2	100